Rituximab and Dupilumab Improve Eosinophilic Granulomatosis With Polyangiitis With Multiple Pulmonary Thrombi

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Case report

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Abstract

Background

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by a necrotizing vasculitis with tissue and peripheral blood eosinophilia affecting small and medium-sized arteries, capillaries, and veins. Venous thromboembolic events have occurred in 19 of 232 (8.2%) patients with EGPA. However, there are only a few reported cases of EGPA complicated by pulmonary embolism or infarction.

Case presentation

We report the case of a 43-year-old woman with eosinophilic granulomatosis with polyangiitis patient with acute respiratory and heart failure due to bilateral pulmonary artery thrombosis and left femoral vein thrombosis in addition to cardiac involvement as myocarditis, pericardial effusion, and diastolic dysfunction, gastrointestinal symptoms and peripheral neuropathy 12 years after disease onset. The condition was refractory to treatment with systemic corticosteroids, intravenous cyclophosphamide, and mepolizumab, but the acute cardiac failure associated with the thrombosis, cardiac and gastrointestinal symptoms, and multiple polyneuropathy improved after a switch to rituximab. But her heart failure did not improve sufficiently, she continued to need oxygen inhalation at 1 L/min and asthma exacerbations occurred. We changed the patient's treatment with mepolizumab to dupilumab. Not only did she have no asthma attacks after switching to dupilumab, but also her vasculitis symptoms improved. Oxygen therapy was discontinued as heart failure improved five months after starting the dupilumab.

Conclusions

This may be the first case report of the successful treatment of pulmonary thromboembolism associated with EGPA by rituximab. In addition, in this patient, treatment with dupilumab was effective not only for the asthma symptoms but also for the symptoms of vasculitis.

Background

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by a necrotizing vasculitis with tissue and peripheral blood eosinophilia affecting small and medium-sized arteries, capillaries, and veins [1]. Venous thromboembolic events have occurred in 19 of 232 (8.2%) patients with EGPA [2]. However, there are only a few reported cases of EGPA complicated by pulmonary embolism or infarction [3-5]. Here, we report the case of a female EGPA patient with acute respiratory and heart failure due to bilateral pulmonary artery thrombosis and left femoral vein thrombosis 12 years after disease onset. The condition was refractory to treatment with systemic corticosteroids, intravenous cyclophosphamide (IVCY), and mepolizumab, but the acute cardiac failure associated with the thrombosis improved after a switch to rituximab and dupilumab.

Case Report

A 43-year-old Japanese woman had had bronchial asthma since age 3 years, atopic dermatitis since age 13, and allergic rhinitis since age 1. She experienced asthma exacerbations several times a year and had been treated with short-acting b-stimulants as needed from age 20 onward. At age 29, she developed a persistent fever of 37.8 °C, general malaise, headache, abdominal pain, diarrhea, orbital pain, dyspnea, and chest pain. Two months later, she experienced paralysis and numbness in the right hand and both lower limbs and discomfort in the left fingertips. Laboratory tests at the time of onset of these additional symptoms revealed leukocytosis (8940/μL, 20.0% of which were eosinophils) and a positive myeloperoxidase – anti-neutrophil cytoplasmic antibody test (21 U/mL). Chest computed tomography (CT) showed no abnormalities in the lung field, but trans-bronchial lung biopsy showed interstitial pneumonia with eosinophil infiltration, and bronchoalveolar lavage showed 27.7% eosinophils. A small rash was found on the left thigh; skin biopsy showed perivascular eosinophil infiltration. Upper and lower gastrointestinal endoscopy revealed dark red signs in the stomach and duodenum, but no endoscopic abnormalities were present in the lower gastrointestinal tract. Biopsy revealed submucosal infiltration of eosinophils in the stomach, duodenum, appendix, and descending colon. Echocardiography showed an ejection fraction of 56.5%, pericardial effusion, pericardial thickening, and diastolic dysfunction. Cardiac scintigraphy with iodine-123-labeled MIBG (metaiodobenzylguanidine) revealed cardiac involvement, appearing as spotty accumulation of MIBG in the anterior wall region and the interventricular septum. The patient was diagnosed according to the Japanese diagnostic criteria for AGA/CSS (allergic granulomatous angiitis/Churg-Strauss syndrome) as having EGPA [6]. After treatment with pulsed methylprednisolone (1000 mg intravenously daily for 3 consecutive days) followed by 50 mg/day orally of prednisolone (PSL), the mononeuritis multiplex, as represented by paresthesia in both lower limbs and numbness in the right hand, and the cardiac involvement, as indicated by general malaise, chest pain, and dyspnea, gradually improved. The woman remained in remission for 5 years on PSL 7.5 mg and the number of eosinophils was 274-707/μL (leukocyte count 6690-8840/μL). However, 6 years after diagnosis she relapsed with chest pain, abdominal pain, and paralysis and numbness in the right hand and numbness in both lower limbs. The number of eosinophils was 314/μL (leukocyte count 8,980/μL; 3.5% of which were eosinophils). We increased her daily PSL dose to 20 mg and added 50 mg of azathioprine increasing to 100 mg, as well as intravenous immunoglobulin (IVIG) (400 mg/kg for 5 consecutive days) several times at a 3- or 4-month interval, but her vasculitis, heart, and gastrointestinal symptoms and peripheral neuropathy did not improve, and she sometimes had asthma exacerbations. The patient's dose of PSL was increased to 30 mg, the azathioprine treatment was switched for IVCY (600 mg/m^2) every 3 to 4 weeks, and once monthly IVIG at the abovementioned dose and monthly mepolizumab 300 mg were added 10 years after diagnosis. However, the vasculitis symptoms did not improve and the patient developed heart failure, requiring oxygen at 7 L/min (Figure 1). We confirmed the presence of thrombi in both pulmonary arteries and the left common femoral vein on contrast-enhanced CT (Figure 2a), as well as multiple regional decreased blood flow in both lungs, predominantly on the right side, on lung perfusion scintigraphy (Figure 3a) 12 years after diagnosis. The number eosinophils did not increase (leukocyte count 11,080/μL; 0% of which were eosinophils).

The patient's IVCY was changed to rituximab 500 mg once a week for 4 weeks, in addition to 3 mg per day of warfarin potassium and continued treatment with PSL 30 mg/day and IVIG every 1 to 2 months. Mepolizumab 300 mg/month was added. Her heart failure began to improve, and 2 weeks after the initiation of rituximab her oxygen demand had decreased from 7 L/min to 3 L/min. However, her symptoms of cardiac involvement and peripheral neuropathy and her gastrointestinal symptoms remained. She received treatment with four courses of rituximab (once weekly for 4 weeks every 6 months), but her heart failure did not improve sufficiently and she continued to need oxygen inhalation at 1 L/min; asthma exacerbations occurred frequently despite the administration of mepolizumab and there was no overall improvement of the symptoms due to vasculitis. The number eosinophils did not increase (leukocyte count 8,700 to 11,800 /μL; 0.4 to 0.9% of which were eosinophils).

We changed the patient's treatment with mepolizumab 300 mg/month to dupilumab 300 mg every 2 weeks to treat the asthma exacerbation 14 years after the diagnosis. Not only did she have no asthma attacks immediately after switching to dupilumab, but also her vasculitis symptoms, such as residual abdominal pain, dyspnea on effort, and leg edema, numbness, and paralysis, improved. Oxygen therapy was discontinued as the patient's heart failure improved five months after starting the dupilumab. She was able to reduce the daily dose of PSL to 25 mg (Figure 4).

The thrombi in bilateral pulmonary arteries and the left common femoral vein had improved by 1 month after rituximab initiation (Figure 2b) and the thrombus in the common femoral vein had disappeared by 3 months after rituximab initiation (Figure 2c). The thrombus in the right pulmonary artery had disappeared by 1 year after rituximab initiation (Figure 2d), and the thrombus in the left pulmonary artery had disappeared by 2 years and 2 months (at 4 months after the change from mepolizumab to dupilumab) after the start of rituximab (Figure 2e). However, some multiple regional decreased blood flow on lung perfusion scintigraphy remained 2 years and 2 months after rituximab initiation (Figure 3b).

Discussion

It has been reported that 65.6% of venous thrombi in ANCA-related vasculitis occur within 1 year of diagnosis [7]. Patients with EGPA complicated by pulmonary embolism have been treated with systemic corticosteroids or cyclophosphamide, or both [3–5], and rituximab can induce remission in patients with relapsing or refractory EGPA [8]. However, to our knowledge, there have been no reports of the effectiveness of rituximab in EGPA patents with pulmonary thromboembolism. Moreover, we have found only one report of success with dupilumab for EGPA, in two pediatric cases (a 13-year-old boy and a 16-year-old girl) [9]. Here, we encountered a rare case of pulmonary thromboembolism 12 years after the onset of EGPA. This may be the first case report of the successful treatment of pulmonary thromboembolism associated with EGPA by rituximab. In addition, in this patient, treatment with dupilumab was effective not only for the asthma symptoms but also for the symptoms of vasculitis.

We obtained this patient's written informed consent to publish.

Abbreviations

CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; PSL, prednisolone

Declarations

Ethics approval and consent to participate; The hospital ethics committee approved the study in accordance with the Helsinki Declaration. The ethics committee at our hospital approved the study, and written informed consent was obtained from all patients or their legal representatives. The ethics approval number was 30-013 at Hiratsuka City Hospital

Consent for publication; Consent for publication was obtained from the patient

Availability of data and materials; Not applicable

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Figures

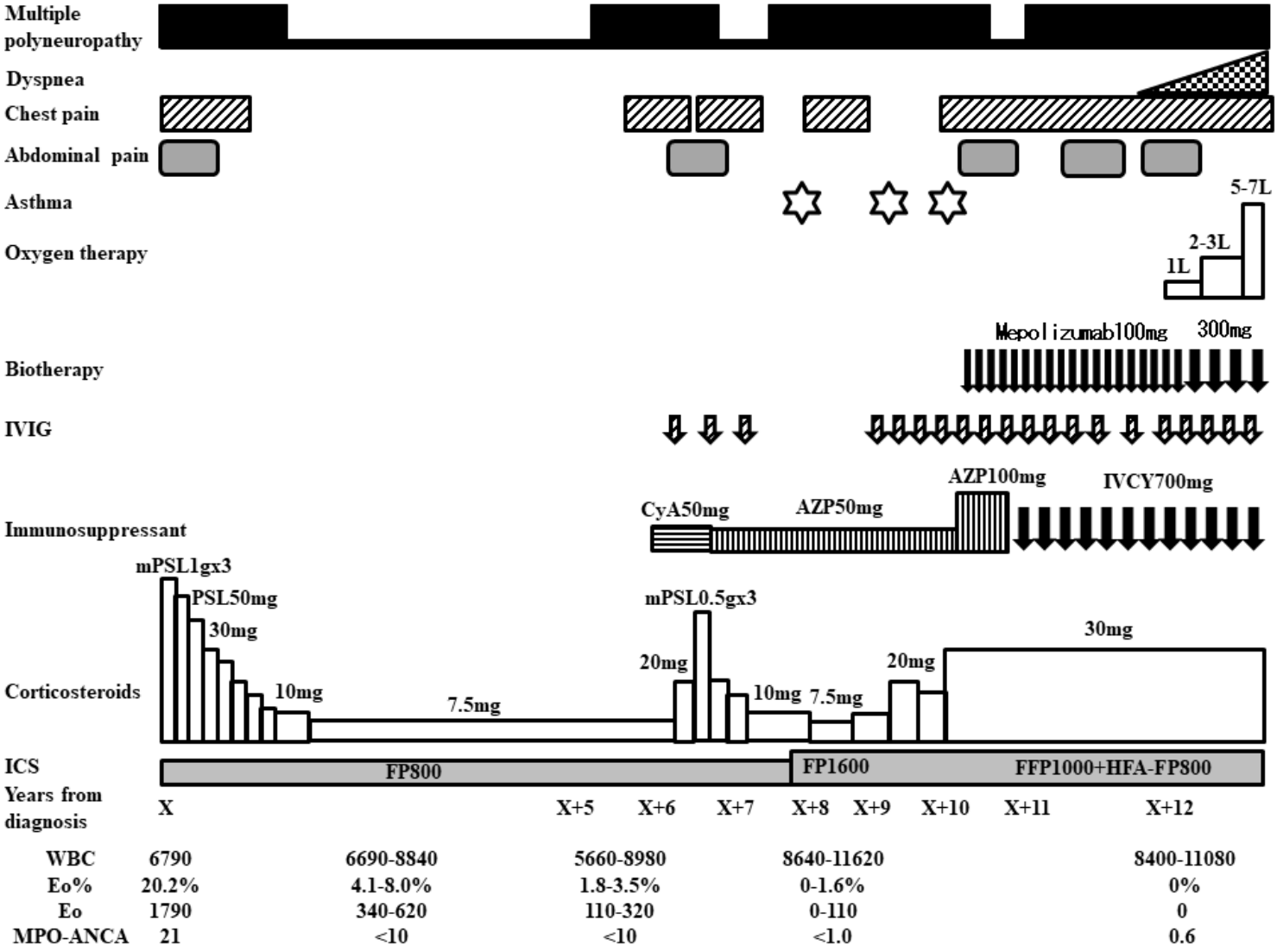

Figure 1

Clinical course from the diagnosis of EGPA to heart failure.

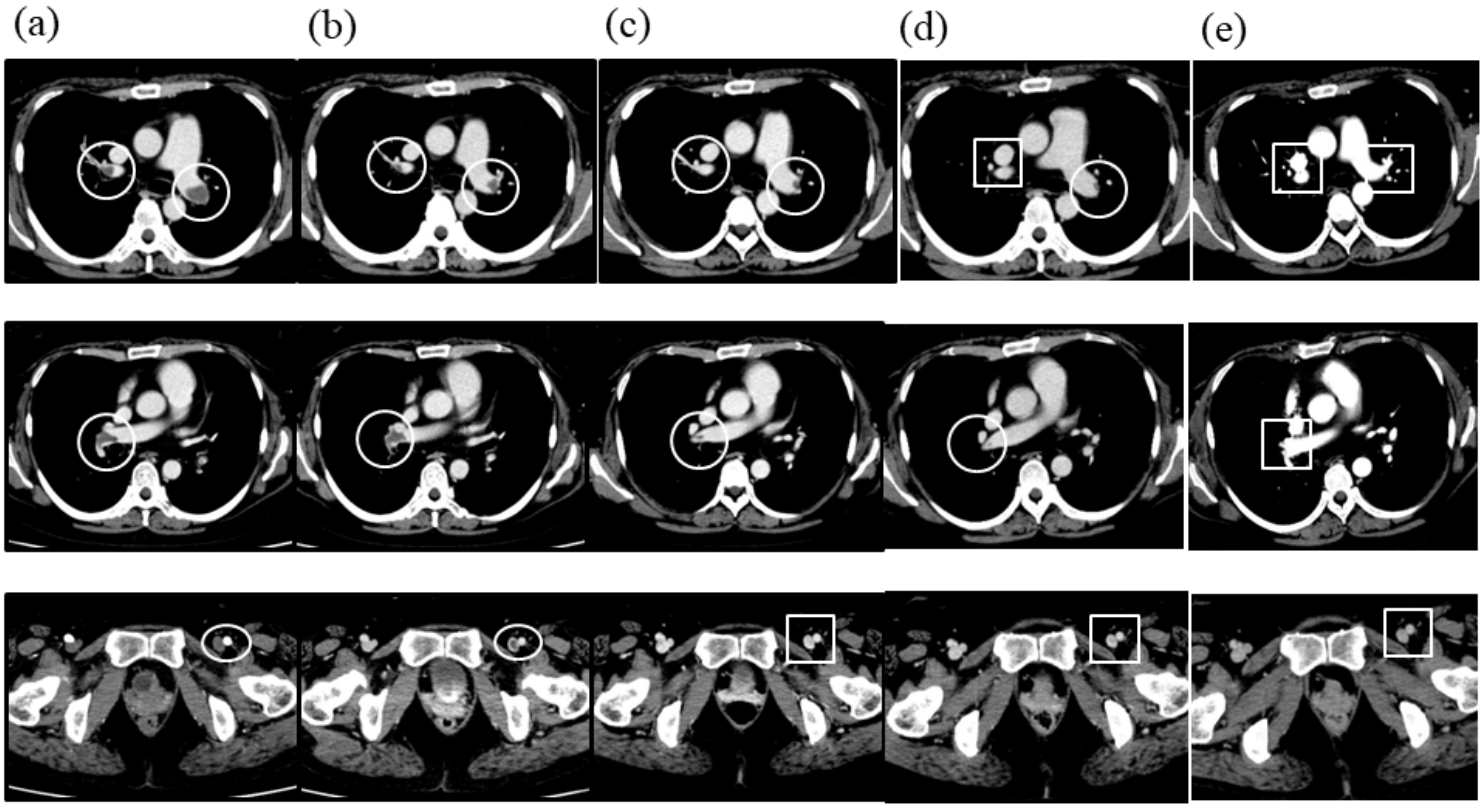

Figure 2

Rituximab-associated changes in bilateral pulmonary artery thrombi and left common femoral vein thrombus on contrast-enhanced computer tomography (CT). Contrast-enhanced CT images before rituximab initiation (a), immediately after the first course of rituximab (500 mg/week for 4 weeks, repeated 6-monthly) (b), and at 3 months (c); 1 year (d); and 2 years 2 months follow-up (e). The thrombi observed before rituximab initiation immediately started to improve with rituximab therapy. Open circles, thrombus present; open squares, thrombus has disappeared.

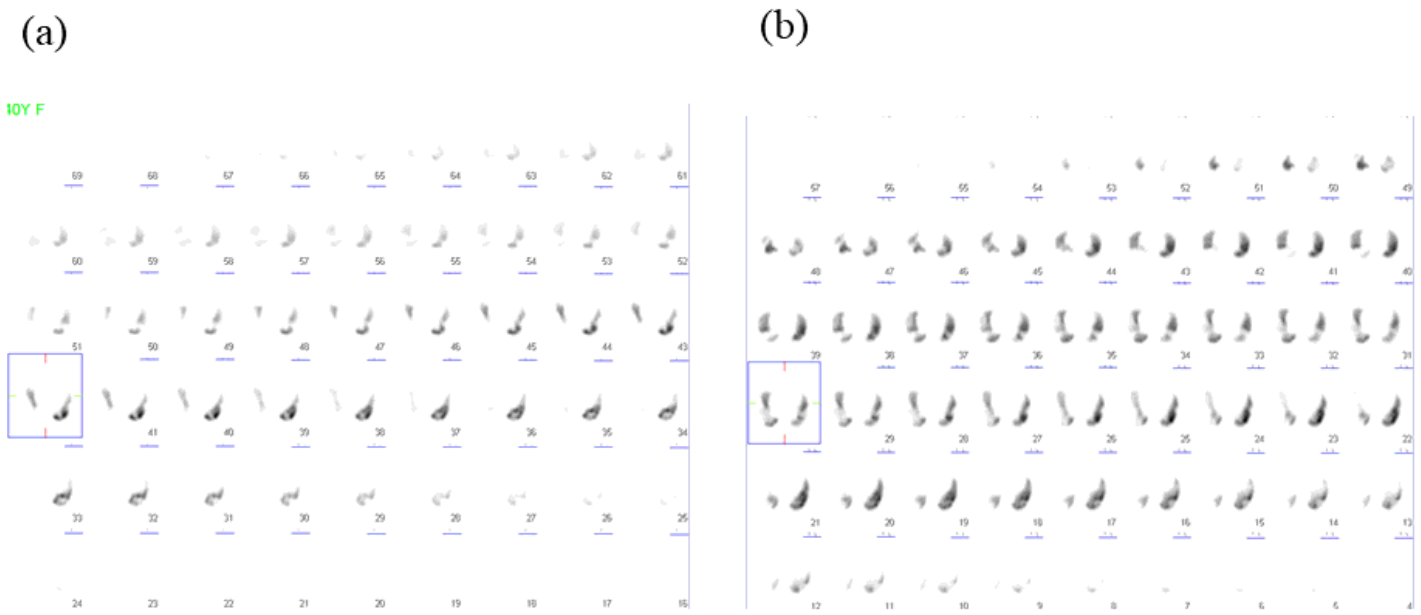

Figure 3

Lung perfusion scintigraphy before and after rituximab initiation. There were multiple regional areas of decreased blood flow in both lungs, but predominantly on the right side, before rituximab administration (a). Two years and 2 months after rituximab initiation, blood flow had improved but some areas of decreased flow remained (b).

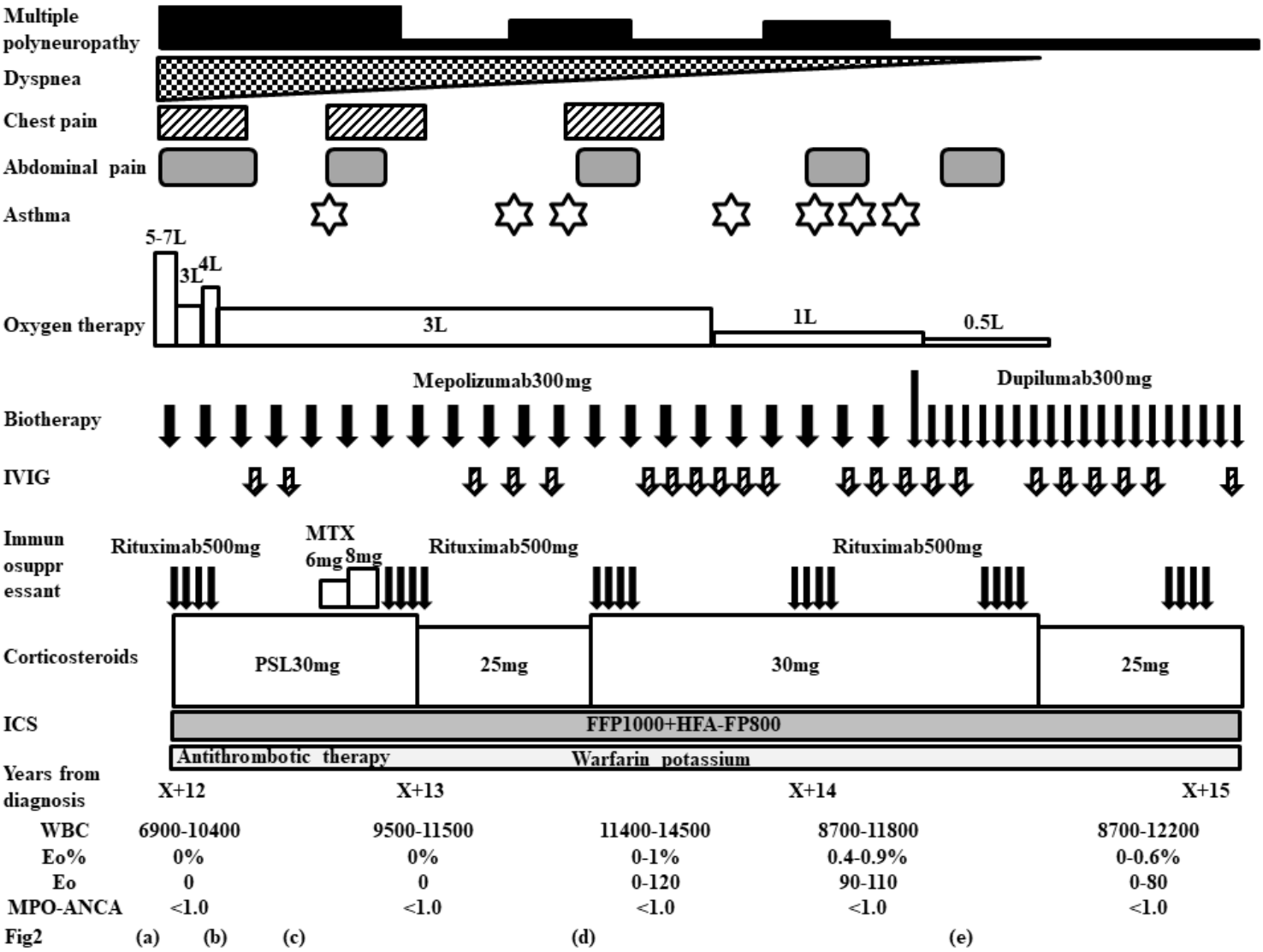

Figure 4

Clinical course from the development of thrombi in bilateral pulmonary and last examination.